REMARKS

Claims 1-14 were pending in the application. Claims 2-3 and 11 have been withdrawn, and claims 4-5, 10, and 12 have been amended. Claims 7-9, 13 and 14 have been cancelled herein, without prejudice, as being drawn to a non-elected invention. New claims 15 and 16 have been added. Accordingly, after the amendments presented herein have been entered, claims 1, 2-6, 10-12, and 15-16 will remain pending. Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. In particular, support for new claims 15 and 16 can be found in Figure 1 and at page 9, lines 6-8 of the specification.

No new matter has been added. Any amendment and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Species Election

It is the Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits has been required, to which the claims will be restricted if no generic claim is finally held allowable. Applicants further understand that upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent from or otherwise include all the limitations of an allowed generic claims as provided by 37 C.F.R. §1.141 *et seq.*

Sequence Listing

In compliance with M.P.E.P. 2422.02, Applicants have amended the Brief Description of the Drawings to indicate the appropriate sequence identifiers for the sequences set forth in the Figure 4A. Please insert after the last page of the specification and following the Abstract, the Sequence Listing submitted herewith, which contains SEQ ID NOS:1-547. No new matter has been added.

Objection to the Drawings

The Office Action indicates that new corrected drawings are required. Applicants submit herewith corrected Figure 4A, and respectfully request reconsideration and withdrawal of the objection to the drawings.

Rejection of Claims 1-6 and 10-12 Under 35 U.S.C. §112, First Paragraph

Claims 1-6 and 10-12 have been rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse the foregoing rejection on the grounds that, based on the teachings in Applicants' specification, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation.

At the outset, the Office Action indicates that the scope of all of the rejected claims specifically excludes the use of an "hR2 sequence," and that the scope of this exclusion is unclear because "the prior art is silent with respect to any sequence in the CTLA4 gene that is called the hR2 sequence." Applicants have addressed this rejection in detail in the section pertaining to the section 112, second paragraph rejection. In brief, the parent application, Application Serial No. 09/534,061, which was incorporated by reference in the present application, provides the hR2 sequence in SEQ ID NO:56. Accordingly, Applicants respectfully submit that the scope of the claimed invention is clear and request withdrawal of the rejection.

The Office Action notes that Applicants provide 122 putative PMR sequences that are "within the human costimulatory receptor locus" and the claims encompass the use of any PMR sequence within this locus. However, according to the Office Action, "[t]he specification does not define any clear ends of the locus, and thus the scope of the claims encompasses the use of PMR sequences that are upstream or downstream of the 318 kb that applicant screened, considering the possible breath of the term 'locus.'" In addition, the Office Action states,

> [i]n order to utilize even the disclosed polymorphic sequences within the broadly claimed invention, one would have to first determine allelic variation within the PMR, which may or may not exist as these have not been screened within populations to demonstrate that the sequences referred to by applicant as PMR are in fact polymorphic within any or all human populations.

Applicants traverse the foregoing rejection on the grounds that Applicants have specifically defined the term "costimulatory receptor gene locus" to include "the genetic region comprising the genes encoding the costimulatory receptors CD28, CTLA4, and ICOS. This locus spans approximately 300 kb on chromosome 2q33" (see page 9, lines 6-8 of the specification). In addition, Figure 1 provides a sequence diagram of the human 2q33 costimulatory receptor region. New claims 15 and 16 have been added to further clarify the claimed human costimulatory receptor region.

Furthermore, the instant specification teaches several approaches for identifying PMR sequences within the costimulatory receptor gene locus (see, for example, the section entitled "PMR Sequences in the Costimulatory Receptor Locus" at page 11, line 5 through page 13, line 16 of the specification). It is well-known in the art that polymorphisms in the CTLA-4 gene have been linked to various autoimmune diseases. Here, Applicants have surprisingly found novel PMR markers that are more closely linked with certain autoimmune disorders or conditions. As described in Example 5, which provides an analysis of microsatellite polymorphisms, use of the novel PMR sequences of the invention can provide a different distribution of polymorphisms than those obtained using the hR2 marker, indicating that the novel PMR markers can be used to further refine genetic alleles linked to the costimulatory receptor locus. Nevertheless, the Office Action in effect would impose an additional requirement for enablement, a requirement not found in the statute; *i.e.*, a working example for every claimed embodiment. However, Applicants assert that a working example is not a requirement for enablement (See, *Shanks v. Scheffer*, 204 U.S.P.Q. 781, 783 (Pat. Bd. Inter. 1979). Moreover, "there is no magical relation between the number of representative examples and the breadth of the claims." *In re Borkowski and VanVenroy*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Section 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it." Hence,

it is not necessary for Applicants to provide *every* polymorphic sequence within the claimed invention.

The Office Action further indicates that with respect to claims 10-12, one would not know how to use the claimed invention. In particular, the Office Action concludes that undue experimentation is necessary to practice the claimed invention because,

> absent some disclosure of a relationship between the detected PMR with a disease, condition or phenotype, it would be highly unpredictable how to utilize the claimed invention, beyond as a tool to study the markers themselves...the specification does not provide any guidance concerning which alleles of which polymorphisms are associated with which autoimmune disorders or conditions.

Applicants traverse the foregoing rejection. It is well-know in the art that polymorphisms in the 3' UTR of CTLA4 have been linked to a number of autoimmune genetic diseases. For example, Applicants disclose that

> [***p**]olymorphisms in the CTLA-4 gene have been linked to various autoimmune diseases*, such as insulin-dependent diabetes mellitus (IDDM) (Witas *et al.*, Biomedical Letters 58: 163-168, 1998); Addison's disease, Graves' disease and autoimmune hypothyroidism (Kemp *et al.*, Clin. Endocrinol. 49:609-613, 1998); myasthenia gravis and thymoma (Huang *et al.*, J. Neuorimmunol. 88:192-198, 1998); lupus (Mehrian *et al.*, Arthritis Rheum. 41:596-602, 1998); thyroiditis, particularly postpartum thyroiditis (Waterman *et al.*, Clin. Endocrinol., 49:251-255, 1998); rheumatoid arthritis (Seidl *et al.*, Tissue Antigens 51:62-66, 1998); Hashimoto's disease (Barbesino *et al.*, J. Clin. Endocrnol. and Metab. 83:1580-1584, 1998); coeliac disease (Djilali-Saiah *et al.*, Gut 43:187-189, 1998); and leprosy (Kaur *et al.*, Hum. Genet. 100:43-50, 1997).

In addition, as described in the Examples, use of the polymorphic sequences of the invention as markers can provide a different distribution of polymorphisms than those obtained using the hR2 marker, indicating that the ***polymorphic elements disclosed herein can be used to further refine genetic alleles linked to the costimulatory receptor locus***. Specifically, Example 5 provides a working example for identifying additional markers in this region that may serve to refine the associations between genetic diseases and the costimulatory receptor region of 2q33. In this regard, Applicants teach that

> 25 microsatellite repeat sequences in the BAC 22700 clone were analyzed for the presence of repeat unit polymorphisms. Following genomic DNA PCR amplification of 13 individuals, the data revealed 4 microsatellites, corresponding to di-, tri- and hexanucleotide repeats, that demonstrated allelic polymorphisms upon analysis by denaturing acrylamide gel electrophoresis (Figure 3). Of the 4 polymorphic microsatellite repeats examined, repeat SARA 31(nt. 263,177-263,211; [ATTTTTT]n6) was represented by 2 alleles, repeat SARA 1(nt. 217,444-217,492; [TCTA]n12) was represented by 4 alleles, while SARA 43 (nt. 125,845-125,892 [GT]n24, homologous to sequences within D2S307) and SARA 47 (nt. 295,275-295,326; [GT]n15) appeared to be highly polymorphic with at least 6 different alleles within 13 individuals examined. Analysis of the 13 individuals for the polymorphisms associated with the known CTLA4 3' UTR (nt. 209,177-209,216; [AT]n40) microsatellite repeat demonstrated 2 alleles. Compilation and comparison of the 4 polymorphic microsatellite alleles found in these individuals revealed no shared allelic combination, ***indicating that this set of 4 polymorphic markers may be effectively applied to the high resolution discrimination of genetic associations of disease states linked to the costimulatory receptor region*** (see page 60, line 27 through page 61, line 10 of the specification).

Based on the foregoing, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-6 and 10-12 Under 35 U.S.C. §112, Second Paragraph

Claims 1-6 and 10-12 have been rejected as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Office Action states that the recitation of "wherein the PMR sequence is not an hR2 sequence" is indefinite because the specification nor the claims "define what is 'an hR2 sequence' or how to identify one."

Applicants respectfully traverse the aforementioned rejection on the grounds that the instant claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the parent application, Serial No. 09/534,061, which was incorporated by reference into the instant application, specifically teaches the hR2 sequence.

> The hR2 DNA segment (nucleotides 6561-6623 of SEQ ID NO: 56) in the human CTLA-4 locus was located 507 base pairs downstream of the

> termination codon and consisted of 32 (AT) repeats with one base pair substitution. This well characterized hR2 repeat has been used extensively in genetic studies in testing the linkage of CTLA-4 to numerous autoimmune diseases in humans. In a preferred embodiment, a PMR of the invention does not include the hR2 repeat (see page 16, second full paragraph of Application Serial No. 09/534,061).

In view of the definition in Applicants' specification, the skilled artisan would find the term "hR2 sequence" to be clear and definite. Accordingly, Applicants respectfully request that the aforementioned rejection be reconsidered and withdrawn.

Rejection of Claim 10 Under 35 U.S.C. §102(b)

Claim 10 is rejected under 35 U.S.C. §102(b) as being anticipated by Weber (U.S. Patent No. 5,582,979). According to the Office Action,

> Weber teaches a method for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject…Weber teaches a dinucleotide repeat polymorphism Mfd36 that is within the D2S72 locus and a method for detecting this repeat. The instant specification teaches that the D2S72 locus is within the human costimulatory receptor locus. Thus, the teachings provided by Weber meet the limitations of the instant claims.

Applicants respectfully traverse the foregoing rejection for the following reasons. For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 10, as amended herein, is directed to a method for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject, said method comprising detecting the polymorphic microsatellite repeat (PMR) of SEQ ID NO:354 in the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence, to thereby determine the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject.

Weber does not teach the PMR set forth in SEQ ID NO:354, as claimed. Hence, Weber does not teach each and every element of the claimed invention. In view of the

foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

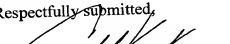
SUMMARY

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. GNN-5343CP2 from which the undersigned is authorized to draw.

Dated: June 10, 2004

Respectfully submitted,

By 

Cynthia Kanik
Registration No.: 37,320
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants